Remarks

Summary of Examiner's Interview

The Applicant thanks the Examiner for his courtesy in granting a telephonic interview on November 19, 2003. Applicant wishes to clarify certain issues in the Examiner's Interview Summary.

The Interview Summary states that "applicant was aware of possible relevant prior art." To clarify, the statement referred to the inventor of the instant application, Dr. Malcolm Simons. As of the interview date of 11/19/03, Applicant's representative (Mr. Nakashima) had not engaged in any direct communication with Dr. Simons concerning any alleged prior art. Rather, Dr. Simons had discussed with another individual the possibility that Dr. Simons might be in possession of relevant prior art. Applicant's representative heard this assertion indirectly, but had been unable to contact Dr. Simons directly to confirm or refute the assertion. As indicated in the Interview Summary, Dr. Simons is presently living in New Zealand and does not have a fixed address, making communication difficult. As also indicated in the Interview Summary, Dr. Simons is terminally ill, further complicating attempts to communicate with him.

Subsequent to 11/19/03, Applicant's representative was able to reach Dr. Simons by telephone to discuss this issue. After reminding Dr. Simons of his ongoing duty of disclosure under 37 C.F.R. §1.56, Applicant's representative requested that Dr. Simons immediately provide copies of any prior art publications in his possession that were material to the patentability of the pending claims, so that they could be submitted in a supplemental Information Disclosure Statement.

Dr. Simons stated that he was not in possession of any prior art publications material to the patentability of the pending claims and that his earlier statements must have been misunderstood. Dr. Simons further stated that any prior art publications of which he was in possession, not already of record in the present case, may be relevant to the claims of issued U.S. Patent Serial No. 5,612,179, not to any claims pending in the instant application. As the '179 patent has already issued, Dr. Simons duty of disclosure with respect to the '179 issued claims is

terminated. Applicant notes that the scope of the pending claims differs from that of the issued claims of the '179 patent.

As indicated in the Interview Summary, terminal disclaimers with respect to issued U.S. Patent Serial Nos. 5,612,179 and 5,192,659 were prepared and filed subsequent to the Examiner's Interview and are now of record in the case, obviating the obviousness-type double patenting rejection.

Further pursuant to Applicant's ongoing duty to disclose, Applicant hereby discloses that the '179 patent, of which the instant application is a continuation, is presently the subject of a patent infringement litigation in the federal district court for the Northern District of California, wherein Genetic Technologies Limited (assignee of the instant application) is the plaintiff and Applera Corporation is the defendant. Applicant is preparing a supplemental Information Disclosure Statement, containing certain documents of record in that litigation, including plaintiff's Complaint and First Amended Complaint, defendant's Answer, defendant's Preliminary Invalidity Contentions and copies of cited references that were not already of record in the instant application. Applicant further discloses that the '179 patent was also the subject of a patent infringement litigation in the federal district court for the Northern District of California, wherein Genetic Technologies Limited (assignee of the instant application) was the plaintiff and Covance/Variagenics(Nuvelo) were the defendants. That litigation has settled. Copies of the complaint and answer from the Covance litigation will also be submitted on a supplemental Information Disclosure Statement.

Rejection of Claims Under 35 U.S.C. §112, First Paragraph

Pending claims 1-3, 5-9, 11-15, 17-21, 23 and 25-46 were rejected under 35 U.S.C. §112, first paragraph as failing to comply with the enablement requirement. Applicant respectfully traverses the rejection. The Examiner's Interview Summary referred to the disclosures of Canck *et al.* (US 2002/0197613 A1) and Baxter-Lowe *et al.* (US 6,194,147) as relevant to the pending enablement rejection.

The Action (mailed 8/21/03) stated that, "From these examples, the specification has been found to enable analysis of the human HLA DQA1 locus whereby the allele for cystic

fibrosis can be detected. The specification has not been found to set forth a reproducible procedure whereby any haplotype of any life form can be determined, much less identify whether the life form is susceptible to any given disease. In order to practice such a method, the skilled artisan would need appropriate starting materials, e.g., primers, as well as conditions under which they are to be used. Seemingly applicant is attempting to avoid disclosing the requisite starting materials by disclosing a general approach to producing primers. While such a disclosure may go towards fulfilling enablement requirements for a method of producing primers, the claimed method is not directed to a method of selecting primers. Rather, one must already have in their possession such essential starting materials, and knowledge of the reaction conditions under which they are to be used."

Baxter-Lowe et al.

The Action referred to Baxter-Lowe et al. for the proposition that:

> The polymerase chain reaction (PCR) process, as described in Mullis U.S. Pat. No. 4,683,202, issued Jul. 28, 1987, allows the amplification of genomic DNA and has given rise to more convenient HLA typing procedures. HLA-DQ alpha and HLA-DP alpha and beta genes have been amplified, and then sequenced or hybridized with oligonucleotide probes. See Saiki et al., Nature, Vol. 324, pp. 163-166, 1986, Bugawan et al., J. Immunol., Vol. 141, No. 12, pp. 4024-4030, 1988, and Gyllensten et al., Proc. Natl. Acad. Sci. USA, Vol. 85, pp. 7652-7656, 1988. However, these methods have limited reliability due to the tendency of the probes to bind with greater or lesser specificity depending on the reaction conditions employed.

Applicant initially notes that Baxter-Lowe referred to the disclosures of Mullis (4,683,202), Saiki et al. (1986), Bugawan et al. (1988) and Gyllensten et al. (1988), not to the disclosure of Simons (*e.g.,* U.S. 5,192,659 and 5,612,179). Nowhere does Baxter-Lowe assert that the methods of Simons are of limited reliability. Each of the cited disclosures predates the priority date of the instant application and by necessity fails to incorporate the teachings of the instant specification. During prosecution of the issued '659 and '179 patents, the disclosures of Mullis, Saiki and Bugawan were distinguished from the inventions claimed in those issued patents. Applicant therefore asserts that the purported lack of reliability of the disclosures of Saiki, Bugawan and/or Gyllensten is not relevant to the reliability of the methods disclosed in the present application.

Applicant further notes that Baxter-Lowe only asserts a limited reliability with respect to probe hybridization methods of HLA allele identification. However, the methods of the instant application are not limited to probe hybridization technique. Rather, the instant application discusses probe hybridization as one of a number of possible techniques that may be used in the practice of the claimed methods. Other possible techniques for DNA analysis, including but not limited to DNA sequencing, primer defined length polymorphism and restriction fragment length polymorphism analysis do not require probe hybridization. The Examples of the instant application disclose the exemplary application of restriction fragment length polymorphism analysis, DNA sequencing and allele-specific amplification for DNA analysis. The cited passage from Baxter-Lowe says nothing about the reliability of such techniques. Several such techniques provide an internal consistency check, which would address problems of false positives or false negatives asserted by Baxter-Lowe. The skilled artisan would have been well aware that for DNA sequencing, the sequencing of the two complementary strands provides an internal check for accuracy, while in the case of RFLP and allele-specific amplification, the apparent sizes of the DNA fragments generated should be consistent with the sequences of the possible HLA alleles (haplotypes) that could be present.

Applicant respectfully asserts that the person of ordinary skill in the art, combining the teachings of the instant disclosure with general knowledge in the art, would be able to practice the claimed methods without undue experimentation.

With respect to the Action's assertion that amplification primers for all possible loci within the scope of the claimed subject matter might constitute essential starting materials, Applicant notes that issued claim 1 of Baxter-Lowe et al. (US 6,194,147) does not present any apparent limitations within the claim language to the lengths or sequences of the primers to be used, but merely recites "amplifying an HLA sequence of DNA of a human subject...". If anything, Baxter-Lowe discloses fewer exemplary HLA primer sequences than the instant application. Baxter-Lowe lists two primers for the DR Beta sequence and states that "all known HLA-DR alleles can be amplified using these primers under a wide variety of conditions." The skilled artisan reading Baxter-Lowe

would conclude that primer selection and optimization of conditions for primer-based amplification would be matters of routine experimentation for the skilled artisan.

Canck et al.

With respect to the disclosure of Canck et al., the Action recited that:

> The HLA system is the most polymorphic human genetic system yet known. HLA class I genes share a similar structure (from 5' to 3'): a S' untranslated flanking region, a first exon (exon 1) having a length of approximately 73 base pairs, a first intron (intron 1) having a length of approximately 130 base pairs, a second exon (exon 2), having a length of approximately 250 base pairs, a second intron (intron 2), having a length of approximately 272 base pairs, a third exon (exon 3), having a length of approximately 276 base pairs, a third intron (intron 3), having a length of approximately 588 base pairs and a fourth exon (exon 4), having a length of approximately 276 base pairs. Polymorphic substitutions within HLA class I alleles are mostly located in both exon 2 and exon 3, encoding the peptide binding groove of the class I molecule. These polymorphisms make differentiation between alleles achievable through a variety of molecular biological techniques such as sequencing or hybridization with relevant probes. In the current diagnostic kits exon 2 and exon 3 are amplified together, resulting in amplicons of about 1 kb. consisting at least of exon 2, intron 2 and exon 3. Locus-specific primers are available for the amplification of these 1 kb amplicons. However, such large amplicons are difficult to amplify and show secondary structure formation resulting in inefficient hybridization of some probes. In addition, due to the emergence of new HLA-Class I alleles, certain allele combinations cannot be distinguished anymore by the detection of polymorphism's only in exon 2 and exon 3 and additional typing in exon 4 is required. This raises the need for the additional amplification of exon 4, resulting in an even larger amplicon. Therefore, a separate amplification of exon 2, exon 3 and/or exon 4 would be desired resulting in amplification products that enable a more efficient typing of HLA class I alleles. However, as locus-specific primer annealing sites are scarce and cannot be found in exon 2, exon 3 or exon 4, **the separate and locus-specific amplification of exon 2. exon 3 and/or exon 4 of HLA-A, HLA-B or HLA-C is not that evident**. (emphases added)

The citation from Canck appears to point directly to the need for and utility of the instant invention. Canck et al. disclose a method for HLA typing directed to amplification and analysis of **exon** sequences in HLA loci. Canck et al. state that, "locus-specific primer annealing sites are scarce and cannot be found in **exon 2, exon 3 or exon 4**, the separate and locus specific amplification of **exon 2, exon 3 and/or exon 4** of the HLA-A, HLA-B or HLA-C is not that evident." (emphasis added)

The difficulties presented by Canck et al. concern the ambiguities present in HLA typing based on **exon** amplification and analysis. It is for precisely that reason that the instant claims recite amplifying, "a non-coding region sequence" and "detecting one or more sequence variants in the non-coding region". The difficulties faced by Canck et al. in amplifying and/or analyzing HLA exon sequences are not relevant to the amplification and analysis of non-coding sequence variants. The instant specification states that, "Primer sites are located in conserved regions in the introns or exons bordering the intron sequence to be amplified. The primer-defined DNA sequence contains a sufficient number of intron seqeunce nucleotides to characterize the allele." "The intron sequences provide genetic variations that, in addition to those found in exon sequences, further distinguish sample DNA, providing additional information about the individual organism." "The method of this invention is based on amplification of selected intron regions of genomic DNA." "As used herein, the term 'intron' refers to untranslated DNA sequences between exons, together with 5' and 3' untranslated regions associated with a genetic locus. In addition, the term is used to refer to the spacing sequences between genetic loci (intergenic spacing sequences)...".

Since the claimed methods are directed towards amplification and analysis of **non-coding** region sequences, the fact that Canck et al. observe difficulties in the amplification of exons 2, 3 and 4 merely points to the need for and utility of the instant methods, as does the observation that, "certain allele combinations cannot be distinguished anymore by the detection of polymorphism's only in exon 2 and exon 3". Canck et al. do not disclose any difficulties associated with amplification and analysis of non-coding region sequences.

"Art-Recognized Issues"

Applicant respectfully asserts that the issues posed by Canck et al. and Baxter-Lowe et al. with respect to amplification and probe hybridization of HLA loci are in fact not problems

recognized in the field of HLA typing. Included are two recent publications disclosing actual real-world typing of HLA loci by amplification and DNA-based typing. The article of Hurley *et al.* (*Tissue Antigens* 55:352-8-7, 2000) evaluated the accuracy and reliability of DNA-based typing of HLA-A and HLA-B loci, using sequence-specific primers and/or probes. Samples were obtained from the National Marrow Donor Program. The results of blinded quality control analysis showed an error rate of 1.1% for HLA-A and 1.9% for HLA-B, based on 11,545 HLA-A and 11,428 HLA-B assignments. The study concluded that large-scale based typing of HLA-A and HLA-B at low resolution (e.g., A*01, B*07) is highly accurate, specific and reliable and characterized the level of accuracy as "particularly remarkable", since the QC samples could not be distinguished from 64,180 donor samples tested at the same time in the same laboratories.

A second publication by Noreen *et al.* (*Tissue Antigens* 57:221-9, 2001) concerned validation of DNA-based HLA-A and HLA-B testing of volunteers for the National Bone Marrow Program registry. DNA-based typing was carried out by PCR using sequence-specific oligonucleotide probes or sequence-specific primers. A random sampling scheme was used to select a statistically significant number of individuals for repeat DNA typing. According to the authors, "DNA-based typing correctly typed nearly 99% of the donors at HLA-A, more than 98% and HLA-B, and more than 97% at both HLA-A and -B validating this methodology for registry typing."

Thus, far from being an "art-recognized" issue, DNA-based HLA typing utilizing amplification and sequence specific primers or probes appears to be art recognized as highly accurate and reliable.

After asserting that the instant specification is "essentially silent as how these [above recited] art-recognized issues are to be overcome," the Action urges Applicant to incorporate

limitations to primers of defined size range, producing amplicons of a defined size range. Because the recited "art-recognized issues" are not relevant to the instant claimed subject matter and in fact are not recognized in the art, Applicant respectfully submits that no such limitations are required to satisfy the enablement requirement of §112, first paragraph.

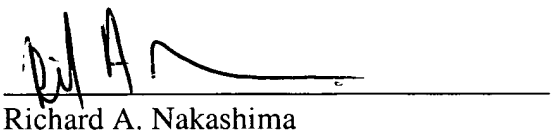
In further support of the absence of any art-recognized issue, requiring identification of primer sequences for all loci to be analyzed within a claimed method, Applicant points, for example, to U.S. Patent No. 6,503,707 (attached) by Baxter-Lowe, issued on January 7, 2003. Claim 1 of the '707 patent recites, "amplifying a genetic sequence of a subject to obtain amplified DNA, which genetic sequence occurs naturally in two or more alleles each characterized by multiple polymorphisms...". Claim 5 of the '707 patent recites, "The method of claim 1, wherein the alleles each characterized by multiple polymorphisms comprise HLA alleles." On their face, those claims contain no limitation as to the sizes of the primers to be used, the amplification conditions or the sizes of the amplicons. Applicant further notes that Baxter-Lowe ('707 patent) only discloses eight exemplary primer sequences to be used.

Applicant respectfully asserts, based on the apparent breadth of the '707 patent claims, the number of examples and the limited number of primer sequences disclosed that the art does not appear to recognize any requirement for undue experimentation with respect to primer selection and design, amplification conditions or the size of the amplicon. Rather, the art appears to consider primer selection and design, amplification conditions and the size of the amplicon to be matters of routine experimentation for the skilled artisan.

Conclusion

Applicant respectfully submits that all pending claims are in condition for allowance and requests an early decision to that effect.

Respectfully submitted,



Dated: December 24, 2003

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